

Review article

J. Perinat. Med.
7 (1979) 55

Liver function and liver diseases during pregnancy

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1 Introduction

Liver diseases during pregnancy comprise an important area of common interest for both perinatologists and internists.

On the basis of my own practical experiences and from an extensive review of the literature which by necessity includes the presentation of at times contrasting views of unsatisfactorily resolved problems, I am attempting to give a review of the current knowledge.

In liver disease as in disease of other organs during pregnancy there are essentially two questions:

1. How is the diseased organ, i.e. the liver influenced by pregnancy – will there be an improvement or deterioration of the disease?
2. What influence has the liver disease on the pregnancy, e.g. in reference to malformations, abortions, prematurity, and perinatal mortality?

2 Changes during normal pregnancy

Every pregnancy is a stress for the entire organism. While the cardiac output increases by 40–50%, the minute volume through the liver remains at 1½ liters/minute. Thus, the relative perfusion of the liver of normally 35% of the cardiac output decreases during pregnancy to 20–25% [22, 27, 37, 77]. Pregnancy poses for the normal liver a functional stress which is tolerated without problems by the normal liver.

Curriculum vitae

GÜNTER SCHOLTES was born 1937 in Aachen, studied in Marburg/Lahn and Berlin and obtained his MD there in 1963. From 1966 to 1977 he worked in the Department for Obstetrics and Gynecology of the Rudolf-Virchow-Hospital Berlin. He qualified as a specialist in Obstetrics and Gynecology in 1970. Since 1977 he is a Lecturer (Privatdozent) at the Free University of Berlin. Since 1978 he is Head of the Department for Obstetrics and Gynecology at the St. Gertrauden-Hospital Berlin. His main field of interest is the whole complex of perinatology, concerning especially the problems of premature labour, twin pregnancy and EPH-Gestosis.



Histologically there are no changes specific to pregnancy in light nor electron microscopy; there are only variances of nuclear size, an increased glycogen content and occasional fat deposition in a few liver cells, especially in the lobular centers [22, 27, 28, 60].

The metabolic stress on the liver from the pregnancy is expressed in some findings deviating from the norm. The interpretation of these changes which are physiologic during pregnancy but abnormal at other times, poses difficulties for the clinician and makes the differential diagnosis of liver disease during pregnancy difficult. (Tab. I reviews the biochemical changes during normal pregnancy.)

Tab. I. Biochemical changes in normal pregnancy

increase	no change		decrease	
	coagulation	thrombocytes	fibrinolysis	
α , β globulines	bilirubin			total protein
urobilinogen		amylase		serum albumin
alkaline phosphatase		prothrombin time		γ globulin
γ GT				cholinesterase
LAP				hemoglobin
	SGOT, SGPT			
	LDH			hematocrit
BSP-retention				
α fetoprotein				
total lipids				
cholesterol				
fibrinogen				
coagulation factors				
(VII, VIII, IX, X)				
sedimentation rate				
leucocytes				

During the entire pregnancy the serum protein concentration is decreased. This is a genuine dysproteinemia rather than a dilution from the hydremia of pregnancy. Until delivery the protein contents falls continuously to levels under 6 g% [37].

Because the albumin decreases and the α - and β -globulines increase, the albumin/globulin ratio decreases from 1.32 before pregnancy to 0.7 at the low point of protein changes on the 4th–6th postpartum day. The γ -globulins also slightly decreased. These changes of the serum protein composition lead to an increased sedimentation rate from the second month of pregnancy on. Coagulation and fibrinolysis are changed typically during pregnancy. During pregnancy the physiological inhibitors of fibrinolysis are increased, the total fibrinolytic activity is slightly reduced [65]. Most coagulation factors, especially fibrinogen, factors VII, VIII, IX, and X are increased. This results in an increased induction of soluble fibrin monomer complexes. The presence of these soluble fibrin monomer complexes in addition to the increase in activity concentration of some plasma coagulation factors is responsible for the slight hypercoagulability during normal pregnancy [53]. The number of platelets is unchanged during normal pregnancy and there are no physiological disturbances of platelet function [44]. The serum bilirubin level is usually in the normal range or

maybe slightly increased because of the greater hemoglobin turnover. It has now been established that bilirubin can pass through the placenta [56]. Tab. II reviews the serum enzymes during pregnancy [16].

Tab. II. Serum enzymes in pregnancy

months of pregnancy	Mean \pm standard deviation*				
	Gamma GT	GOT	GPT	AP	LDH
0	11.7 \pm 4.6	21.9 \pm 7.9	18.6 \pm 6.2	48.5 \pm 12.7	148.4 \pm 26.5
2	13.4 \pm 5.2	27.2 \pm 7.4	23.6 \pm 10.9	41.0 \pm 11.6	141.7 \pm 24.7
3	10.5 \pm 4.4	21.9 \pm 5.8	18.2 \pm 5.5	38.6 \pm 8.4	134.1 \pm 17.4
4	10.5 \pm 6.1	24.7 \pm 10.4	23.8 \pm 10.2	41.1 \pm 9.7	130.3 \pm 19.7
5	13.2 \pm 9.5	24.3 \pm 8.9	22.5 \pm 9.5	49.6 \pm 13.0	127.5 \pm 20.2
6	15.0 \pm 10.5	23.9 \pm 8.4	18.8 \pm 6.4	61.3 \pm 15.8	142.6 \pm 24.1
7	16.1 \pm 10.4	29.9 \pm 11.8	24.8 \pm 12.9	81.1 \pm 26.2	148.3 \pm 27.2
8	22.1 \pm 14.6	31.9 \pm 12.8	27.6 \pm 13.4	114.2 \pm 32.8	159.6 \pm 21.3
9	24.3 \pm 11.5	29.5 \pm 11.4	25.1 \pm 12.6	135.2 \pm 41.2	162.7 \pm 24.2

* The mean probabilities of error are between 0.01 and 0.0005.

Alkaline phosphatase (AP), a mixture of various isoenzymes from liver, bone, small bowel and placenta, markedly increases during pregnancy especially after the sixth month; it drops sharply 24 hours postpartum and is still slightly above normal on the sixth postpartum day [37]. The activity of alkaline phosphatase during late pregnancy is mostly due to the placenta-derived heat-stable phosphatase portions [37, 41, 57].

Gamma-glutamyl-transpeptidase (γ - GT), which occurs along the intra/and extrahepatic bile ducts and is localized in the mitochondria, is the most sensitive test for cholestasis [55]. This enzyme also is increased normally during pregnancy from the sixth pregnancy month on [16].

Leucine-amino-peptidase (LAP) is more specific than the alkaline phosphatase and it is markedly elevated in cholestasis together with γ - GT [15]. It is also increased during the last month of normal pregnancies [77]. The transaminases SGOT and SGPT are the most specific indicators for hepatocellular destruction [9, 37, 55]. Since the integrity of liver cells during pregnancy is generally not compromised SGOT and SGPT remain normal during uncomplicated pregnancies. The data from 304 normal pregnant women illustrated in Fig. 2 show a slight increase of these enzymes during the last three months of pregnancy [16]. During delivery and during the first few days postpartum a slight increase in SGOT and SGPT may be observed [27]. Enzymes indicating necrosis include lactate dehydrogenase (LDH), a relatively nonspecific enzyme, which occurs in addition to liver also in the cardiac and skeletal muscles [55]. From Tab. II a slight increase of LDH in the last two months of pregnancy may be noted [16].

Of interest are enzyme examinations in newborns 24 hours after birth. As an expression of liver cell necrosis in the newborn after fetal heart rate decelerations during birth and after protracted deliveries with the assumption of hypoxic states, there is a significant increase of LDH, SGOT, SGPT and especially GLDH activity [54].

Among the so-called liver function tests during pregnancy only the bromosulphophthalein test (BSP) has a certain validity. The BSP retention after 45 minutes should not exceed 8% in a normal preg-

nancy [22, 26, 42]. It is markedly increased in cholestasis [55].

In more than 60% of pregnancies the so-called cutaneous liver signs such as palmar erythema or spider nevi occur [23]. They are not an expression of liver disease but rather due to the increased estrogen concentration and its vasodilatory effects. These cutaneous liver signs regress completely within 4–6 weeks after delivery.

3 Review of liver diseases during pregnancy

Little can be said as to the prevalence of anicteric liver disease during pregnancy, since in the absence of jaundice as lead symptom an unknown number of liver diseases is not recognized [23]. It has been surmised that during pregnancy, too, anicteric illnesses are more common than icteric ones [45]. Obviously, icteric liver diseases during pregnancy are much better studied and described [23, 30, 37].

Basically, any icteric illness may occur during pregnancy. These cases represent the random co-existence of pregnancy and liver disease. These, therefore, are referred to as icterus in graviditate. In addition, there are liver diseases caused by the pregnancy itself. These have been designated as icterus e graviditate, namely, icterus as a consequence of pregnancy.

Large case collections indicate a prevalence of icterus during pregnancy between .2 and 1.8 per/1000 [28, 30, 33, 45]. Thus, jaundice during pregnancy is a relatively rare symptom.

Of interest is a review by HAEMMERLI (Tab. III) about the incidence of varying forms of icterus, based on 456 cases [34]. A classification of icteric mothers during pregnancy is seen in Tab. IV.

I will now describe separately the severe diseases summarized in Tab. IV. The interaction of liver disease in pregnancy will be emphasized and the question of a possibly necessary termination of pregnancy will be reviewed with each disease.

3.1 Icterus in graviditate

3.1.1 Viral hepatitis

Hepatitis is one of the most common infectious diseases with about 100,000 to 150,000 cases per

Tab. III. Distribution of important causes of jaundice during pregnancy [34]

I. Icterus <i>in</i> graviditate:	58.8%
of these:	
acute hepatitis	41.2%
extrahepatic cholestasis (gallstones, etc)	5.9%
other forms (chronic hepatitis, liver cirrhosis)	11.7%
II. Icterus <i>e</i> graviditate:	34.9%
of these:	
cholestasis of pregnancy	20.5%
acute fatty liver of pregnancy	0.4%
toxemia of pregnancy (hyperemesis, pre-eclampsia)	10.7%
rare forms	3.3%
III. Unclassifiable	6.3%

Tab. IV. Etiology of jaundice during pregnancy

I. Icterus <i>in</i> graviditate
1. Acute viral hepatitis
2. Chronic forms of hepatitis and cirrhosis
3. Rare forms of jaundice
a. intrahepatic cholestasis (e.g. drug-induced jaundice)
b. extrahepatic cholestasis (e.g. gallstones)
c. functional hyperbilirubinemia
d. hemolytic jaundice
e. jaundice with septicemia (severe pyelonephritis, septic abortion with endotoxin shock)
II. Icterus <i>e</i> graviditate
1. Cholestasis of pregnancy (idiopathic jaundice of pregnancy)
2. Acute fatty liver of pregnancy
3. Toxemia of pregnancy (hyperemesis, pre-eclampsia, eclampsia)

year in West Germany with a population of 60 million people. The highest case rate is seen in children under 15 years and in young adults; thus, it includes the early reproductive age range. Acute hepatitis is a clinical syndrome caused by infection with hepatitis virus A and B. The discovery of HB_S-Ag (Australia antigen) in 1965 by BLUMBERG [8] solved one of the main problems of hepatitis research, namely, a serologic classification as to the differentiation of the two infections. Demonstration of HB_S-Ag in blood indicates an acute infection with the hepatitis B virus. Thus, the Australia antigen, or HB_S-Ag, is an indicator for the presence of hepatitis B virus [15]. For hepatitis B there are three separate antigens with numerous

sub-types of which the so-called Australia antigen is the most thoroughly investigated.

Since, it has become possible to serologically document hepatitis A infection there have been indications that there are additional hepatitis organisms, so-called C or non-A-non-B-virus. This "non-A-non-B hepatitis" has become the most common form of post-transfusion hepatitis in the USA. The existence of at least two of these viruses has been discussed, however, there are no laboratory tests for the identification at this time.

For clarification, the various nomenclatures used over the years are given in Tab. V with the older designations in parentheses.

The transmission of hepatitis A occurs primarily by the fecal-oral route. Transmission may also occur parenterally during the viremic stage. Transmission of hepatitis B virus occurs predominately parenterally, though recently it has been recognized that transmission is also possible by sputum or sexual contact. However, these alternate transmission pathways have no major importance. Quantitative analysis has shown that it takes 10–100 liter saliva or 1–10 tons of urine or sweat to accumulate the amounts of HS_SAg contained in 1 ml serum [15].

Incubation time for hepatitis virus A is 2–6 weeks, for virus B 2–6 months. There is immunity against reinfection of the same type but no cross immunity. New studies have shown that infection with one antigen subtype confers no immunity against disease with another subtype.

A description of the illness, laboratory findings, immunological aspects, and therapy will not be given in this obstetrically oriented discussion [4, 6,

Tab. V. Nomenclature of various types of hepatitis

Viral hepatitis type A = viral hepatitis A = VHA = hepatitis A = HA (Infectious hepatitis = IH = hepatitis infectiosa = HI = epidemic jaundice = short incubation time hepatitis). The organism is designated as hepatitis A virus – HAV

Viral hepatitis type B = virus hepatitis B = VHB = hepatitis B = HB (serum hepatitis = SH = homologous serum icterus = long incubation time hepatitis). The organism is designated as Hepatitis B virus = HBV

Viral hepatitis type C = virus hepatitis C
The organism is designated as non-A-non-B-virus

12, 31, 43, 55, 70]. The susceptibility for hepatitis is — in contrast to older opinions — not different during pregnancy [37]. Hepatitis may occur during all phases of pregnancy. In one review [75] hepatitis was found in 13% during the first trimester, in 31% in the second, and in 56% in the third trimester.

If hepatitis begins during late pregnancy, during or after birth several authors have seen a more severe course which converts into the chronic form, than in a comparison group in the same age [11, 22, 32]. However, other authors reported that there were no differences in duration, severity, and fatal outcome of the illness during pregnancy; some even have stated that the course is milder and shorter [1, 4, 33, 45]. **The mortality of hepatitis during pregnancy in this geographic area is not different than the mortality from hepatitis of an unpregnant woman of the same age [1, 33, 45, 50].** Severe cases and high mortality have always been observed if additional risk factors were present [2, 11, 17]. Data from developing countries in Asia and Africa with poor nutritional conditions indicate a maternal mortality of 50–70%. The assumption might be justified that the protein malnutrition during the increased need for protein during pregnancy has an unfavorable influence on the course and outcome of the hepatitis [37]. Proven pathways of the infection with hepatitis on the infant are oral-fecal postpartum, haematogenous infection if the infant is injured during birth, the maternal-fetal microtransfusion in the presence of the placental lesion, and colostrum. A transplacental transmission of hepatitis virus or HB-Ag must be assumed [5, 11, 14, 48, 66]. If the maternal disease occurs during the first trimester the fetal case rate is very low [66]. Evidently during the clinical maternal illness the placental foci are attacked by maternal antibodies before infection of the fetus itself [72]. The risks for neonatal infection increases the closer the maternal hepatitis infection occurs to the delivery date [66, 67]. With illness during the third trimester until two months postpartum HB-Ag presence in the newborn in 70–80% can be shown [66]. **Maternal jaundice regardless of the etiology has no special influence on the fetus because infants of icteric mothers are usually born without marked jaundice.**

Because of its protein-binding bilirubin presumably passes only poorly the placental barrier [52]. **Data on the incidence of abortions vary between reports of no increase [39, 75] and 25% [72] in manifest maternal hepatitis during the first trimester.** Similarly, figures on the incidence of stillbirths vary, with the highest being given as 22.8% [69]. Generally, the rate of stillbirths following hepatitis in the first and second trimester does not differ from that in other pregnancies [36, 39, 75] while stillbirths after hepatitis in the third trimester definitely are increased [75].

By contrast there is a definite increase of prematurity to 15–35%, especially with disease in the third trimester [36, 37, 39, 72, 75]. The incidence of prematurity is the same in infected fetuses or in HB-Ag negative newborns [66, 67]. It is unknown whether this marked increase of prematurity is due to the acute maternal disease or due to the direct effect of the virus on the fetus or placenta.

There is some indication that the premature onset of labor is due to another mechanism because jaundice during pregnancy regardless of its etiology pre-disposes for prematurity [37]. In addition to a disturbance of the metabolism of placental hormones the increase in bile acids and fatty acids might lead to an increased tone of the uterus muscle and thus trigger premature labor [45].

As a consequence of the increased incidence of prematurity, perinatal mortality is increased, primarily postpartum mortality. This is equally true for hepatitis as for all other liver diseases associated with jaundice. The prevention of prematurity in diseases associated with icterus is an urgent obstetrical problem. Tocolytic drugs of the beta-mimetic type are not absolutely contraindicated in liver disease. However, if the estimated fetal weight is above 2000 grams one should not necessarily insist on tocolysis because, given the current progress in neonatal pediatrics, these children have a good to excellent extra-uterine survival chance, especially after fetal lung maturity has been stimulated.

On the other hand RICHTER and WIEST [63] consider hepatitis as a contra-indication for tocolysis because the metabolic action of beta-mimetic additional stress the hepatic metabolism. Whether

this is also valid for cholestatic icterus of pregnancy has not been defined.

Because of the possibility for neonatal infection and the additional stress of the mothers, they should not nurse the infant [13, 37].

The incidence of intrauterine growth retardation and dysmaturity is not increased with hepatitis [36].

There has been much discussion on the possible association between viral hepatitis and fetal malformations. According to TÖNDURY there can be no question about the occurrence of embryonal disturbances from the hepatitis virus. However, a specific syndrome of hepatitis embryopathy has not been described [73]. A number of case reports can be found about malformations in infants whose mothers contracted viral hepatitis during early pregnancy. In a large number of these case reports the correlation appears doubtful [37]. Assuming an incidence of malformation of 2–3% in the general population the malformation rate of 3.5% found in series of 528 cases is not significantly increased [20, 21]. Another series of 555 pregnant women with hepatitis yielded a malformation rate of only 2.6% [39]. Some authors have cited an association between viral hepatitis and mongolism as indication for virus-induced chromosomal changes; however, this has not been proven beyond doubt to date [37, 48, 71, 77].

A special situation occurs if the conception occurs at the time of an acute viral hepatitis. During this phase of hepatitis, cell cultures of peripheral lymphocytes show a 7-fold increased rate of abnormalities with Australia antigen positive hepatitis and a 2-fold increase in patients with Australia antigen negative hepatitis [74]. No practical consequence can be derived from these findings nor from the fact that hematogenous transplacental dissemination of the virus is possible in all stages of pregnancy [72].

It may be assumed as certain that the course of hepatitis is not influenced by either continuation or termination of pregnancy [37]. Termination may not halt the deterioration of a case of hepatitis. Permanent liver damage such as the transition into a chronic form do not occur more frequently in pregnant than in non-pregnant patients.

Acute fulminant viral hepatitis, i.e., acute yellow liver atrophy has a very high mortality of 50–80% even without pregnancy. Termination of pregnancy does not change this prognosis. It usually occurs too late and poses an additional risk [61]. Thus, these facts do not justify termination per se and viral hepatitis with maybe the exception of the extremely acute cases [75].

The prophylaxis of viral hepatitis has seen new aspects in the past few years: For hepatitis A it has been shown that a passive immunization with

- gammaglobulin before and after exposure decreased the incidence of
- hepatitis, mitigate the course and prevents death [15]

The newly available special immune globulin with a high content of Anti-HB_s (Anti-HB_sIg) [18, 58, 68] offers an effective prophylaxis against hepatitis B following exposure and this protection may include the neonatal period [47].

Initial experiences have been made with active immunization against hepatitis B [46].

3.1.2 Chronic hepatitis. Cirrhosis.

Chronic hepatitis may be associated with viral disease, drugs, or of unknown etiology. An immune mechanism has been speculated for the chronic hepatitis of unclear etiology [7, 78].

Clinically cases are divided into chronic persistent hepatitis with a benign course and a chronic active and chronic aggressive hepatitis with often progressive course into cirrhosis.

While the course of chronic persistent hepatitis during pregnancy is not different this is not necessarily true for chronic aggressive hepatitis, and it may vary noticeably in individual cases [23]. Various authors have reported an increase in the incidence of chronic aggressive hepatitis with cirrhosis in relatively young age ranges [40, 51]. Thus, cases with cirrhosis during pregnancy may increase in the future [51].

To date it has been rather rare that a patient with cirrhosis conceived because the disease usually occurred after menopause. Even cirrhotic patients during the reproductive age rarely become pregnant because the disturbed estrogen metabolism leads to secondary infertility in anovulatory cycles.

Indeed, pregnancy in a cirrhotic patient may indicate sufficient liver function [38]. While some authors report a deterioration of the cirrhosis during pregnancy [22, 32], others have not seen a difference on the long-term prognosis and even improvement of the liver function has been noted [38, 51, 59, 77]. The principal risk for the pregnant patient is hematemesis in the presence of portal hypertension and possible gastro-esophageal reflux esophagitis. The prognosis of mother and child is determined by the complications of liver cirrhosis (portal hypertension, ascites, hepatic coma) [39]. About 20% of pregnant patient with cirrhosis experience liver failure [37].

Because of the complications a close contact between obstetrician and hepatologist is necessary, especially with chronic aggressive hepatitis and even more well with liver cirrhosis in order to discuss the question of continuation or termination of the pregnancy. Each case must be analyzed individually.

Immunosuppressive therapy during pregnancy should be discontinued because of the possible effects on the fetus [51, 77].

Steroid treatment of chronic active hepatitis may be continued during pregnancy [51]. However, the assessment of estriol values for the surveillance of the fetal-placental unit is impaired with this medication. In chronic forms of hepatitis and with cirrhosis prematurity (up to 50%), stillbirths (up to 20%) and also neonatal mortality is increased as a consequence of the high prematurity rate [38, 39, 40]. The rate of hypotrophic infants is also increased [39]. Perinatal mortality of mature infants, however, is not increased [37]. Surviving infants do not have liver damage [51] and the rate of malformations is not increased [37, 24], but the rate of abortions is [38, 39]. Delivery under anesthesia which causes stress for the liver, e.g. halothane, should be avoided; regional anesthetics are the alternatives.

Because of the lack of coagulation factors in cirrhotic conditions there may be considerable hemorrhages during the third stage [51].

Chronic aggressive hepatitis and compensated liver cirrhosis pose relative indications for termination of pregnancy while decompensated liver cirrhosis with ascites, esophageal varices, hemorrhages, and early coma, the termination is absolutely indicated.

It should be carried out with the least stressful method [61].

Because of the identical symptoms primary biliary cirrhosis is often confused with the recurring intrahepatic cholestasis of pregnancy [51]. In biliary cirrhosis the prematurity rate and thus perinatal mortality is increased as well. However, the course of the disease is not influenced by pregnancy [61].

3.1.3 Rare forms of icterus

3.1.3.1 Drug-induced jaundice

Numerous cases of jaundice, including those during pregnancy, can be explained by various drugs (antihistamines, antimitotics, sedatives, tuberculostatics, halothane, etc.) [37]. Many of these substances are indirect hepatotoxic which cause liver changes in only a small percent of exposed individuals as an idiosyncrasy. Their action is independent of the dose and occurs after varying duration of the administration. Evidently predisposing factors in the individuals play a role [10]. Morphologic changes in the liver vary greatly [62]. Cases of drug jaundice do not differ in their course or severity during pregnancy [83].

3.1.3.2 Extrahepatic cholestasis

Gall stones and subsequent extrahepatic obstructive jaundice does not occur during pregnancy any more frequently than in non-pregnant patients, nor are symptoms and therapy different [37]. This is also true for inflammatory changes of the bile ducts.

3.1.3.3 Functional hyperbilirubinemia

In functional disturbances of the bilirubin metabolism with hyperbilirubinemia (Tab. VI [76]; of obstetrical interest only groups 1c, 2a, 2b) the complaints increase during pregnancy. Often mild subclinical hyperbilirubinemia become clinically manifest during intercurrent illness, trauma, alcohol abuse, surgery, oral contraceptives, or pregnancy.

There is no treatment for these congenital hyperbilirubinemias regardless of the presence or absence

Tab. VI. Forms of congenital non-hemolytic hyperbilirubinemia [76]

I. Increased unconjugated bilirubin:	
a.	severe hyperbilirubinemia: CRIGLER-NAJJAR Syndrome Type I
b.	moderate to severe hyperbilirubinemia: CRIGLER-NAJJAR Syndrome Type II
c.	mild hyperbilirubinemia: GILBERT's Syndrome
II. Elevation of unconjugated and conjugated bilirubin	
a.	with pigment deposits in the hepatocytes: DUBIN JOHNSON Syndrome
b.	without pigment deposition in the hepatocytes: ROTOR Syndrome
III. With elevation of unconjugated and conjugated bilirubin and elevated bile acids (pruritus). Recurrent intrahepatic cholestasis	
a.	benign course: Type SUMMERSKILL-TYGSTRUP Type AAGENAES
b.	malignant course (cirrhosis): Type CLAYTON-JUBERG (BYLER's disease)

of pregnancy. There is usually no maternal indication for termination of pregnancy. Because of the increased jaundice the rate of prematurity may be slightly increased. Thusfar, about 30 cases of pregnancy in DUBIN JOHNSON syndrome have been described [3, 19].

GILBERT's disease, a relatively harmless metabolic anomaly with slight increase of unconjugated bilirubin up to maximally 5 mg%, is not influenced by pregnancy and nor does it have an effect upon the pregnancy.

3.1.3.4 Hemolytic jaundice

While jaundice usually indicates liver involvement, it may occur without impaired liver function. Thus, there is usually a mild jaundice in the congenital and acquired hemolytic anemias; primarily the unconjugated bilirubin is increased [37].

The association of pregnancy and hemolytic anemia in most cases is a serious complication and termination is indicated in many cases.

It must be taken into account that many forms of hemolytic anemia deteriorate progressively during pregnancy and that severe hemolytic crises may occur [35], especially in the third trimester and during birth. These correlations have been especially well studied in sickle cell anemia. Pregnancy with

this disease is a severe stress with a high maternal [10] and infant mortality (50%) as a consequence of the high prematurity rate [25]. During the deterioration caused by the pregnancy of these hemolytic anemias there is an increased tendency for thrombosis, leading to placental infarction and abruptio. Sickle Cell anemia is an indication for termination of pregnancy as is hereditary spherocytosis and the thalassemias.

3.1.3.5 Other forms of jaundice

Jaundice may occur in the course of complications of pregnancy associated with disseminated intravascular coagulation (endotoxin shock) or in septicemia with severe pyelonephritis. This has to be separated from jaundice with primary liver disease or bile duct disease [37].

Fortunately, the association between pregnancy and liver cell carcinoma is rare, but it is an absolute indication for termination of pregnancy since metastases into the fetus may occur [61]. Individual cases of pregnancy with liver tumors have been described [51].

3.2 Icterus e graviditate

3.2.1 Intrahepatic cholestasis of pregnancy (idiopathic jaundice of pregnancy)

This syndrome has been described under many synonyms in the literature [37]. In the pronounced form there is a visible jaundice and in the moderate variations there is generalized pruritus during pregnancy [37]. Next to viral hepatitis it is the second most common form of jaundice during pregnancy with about 20% [49]. The disease is observed in about 1:500 to 1:10,000 cases [22, 37, 49]. General health is only slightly impaired. The disease usually occurs after the 22nd week of gestation, rarely as early as the first trimester. Symptoms disappear shortly after delivery. These usually reoccur more severely during a subsequent pregnancy. The lead symptom is the generalized pruritus, especially on the trunk and extremities.

The jaundice is rarely severe. Bilirubin levels rarely exceed 5–8 mg% and are predominately direct reacting (conjugated) bilirubin and they become

normal during the postpartum days. Changes typical for cholestasis are seen in laboratory tests. Transaminases are slightly elevated, rarely above 300 units [42]. Histological examinations of liver biopsies in the light microscope demonstrate hepatic stasis with bile thrombi in the dilated bile canaliculi, especially around the central veins. There are no inflammatory reactions or indications of proliferation of mesenchymal cells [37].

The etiology of this disease is not completely understood [49, 51]. Probably it is a disturbance in the estrogen metabolism with a familiar disposition [37, 51], which becomes manifest during pregnancy or with the use of estrogen-containing contraceptives. The illness is harmless for the pregnant patient.

Reports on the prognosis for the child vary. A rate of prematurity of up to 40% explains the high perinatal mortality reported by some [29, 37, 49, 77].

There is no specific treatment and termination of pregnancy is not indicated [61]. The pruritus may be alleviated with the use of cholestyramine, a non-resorbable alkaline synthetic resin which binds bile salts in the intestine [49]. This interrupts the entero-hepatic circulation and the bile acids in the serum fall as a consequence. It is clinically important to rule out viral hepatitis in the differential diagnosis.

3.2.2 Acute fatty liver of pregnancy

This is a fortunately rare, yet very severe, disease described first by STANDER and CRADDEN in 1934 [64]. The etiology is unknown. The disease usually begins very actually in the 36th to 40th week of gestation [37]. First signs, even before nausea and vomiting, are lethargy, depressive mood changes, and psychotic signs. In addition there are frequently neurological symptoms. This psychotic phase which may precede the other symptoms for up to 14 days is considered the typical initial sign of the disease [64]. This may be confused with the equally rare pregnancy psychoses.

Later severe headache, intractable vomiting, — initially bilious, later coffee-ground — as well as abdominal pain. Among the severe problems are acute hemorrhages into the gastrointestinal tract, kidney, central nervous system, as well as the

development of disseminated intravascular coagulopathy. Ultimately, oligouria or anuria occur as well as stupor and coma. The clinical course resembles that of the acute liver necrosis in viral hepatitis with the corresponding laboratory findings [37]. There are 118 cases reported in the literature [64]. Histologically characteristic is a picture of fatty changes at the central veins, with swollen, foamy and packed hepatocytes. The cytoplasm is displaced with numerous small vacuoles [37].

Therapy of fatty liver pregnancy is symptomatic. It includes [64]:

1. termination of pregnancy
2. treatment of hepatic coma
3. correction of imbalance in the metabolism of glucose, fluids, electrolytes and acid-base
4. treatment of coagulopathy

These intensive measures have decreased the mortality of this disease during the last ten years from 80% to 45% [64].

3.2.3 Toxemia of pregnancy

Some women with toxemia of pregnancy have jaundice during the course of hyperemesis gravidarum or eclampsia. These forms of jaundice constitute accompanying symptoms of the underlying toxemia. A specific therapy of this form of icterus is not possible nor is it necessary since the jaundice will disappear together with the underlying toxemia.

4 Liver disease and termination of pregnancy

Tab. 7 reviews indications for termination of pregnancy in relative and absolute terms according to literature data. Thus, there is an absolute indication with

1. acute fatty liver of pregnancy,
2. decompensated liver cirrhosis,
3. liver carcinoma

Relative indications are:

1. chronic aggressive hepatitis,
2. compensated liver cirrhosis,
3. primary bilious cirrhosis,
4. some hemolytic anemias

Tab. VII. Indications for termination of pregnancy in liver disease

Disease	Indication		Increased pre-maturity rate/ increased perinatal mortality	Influence on the infant
	Relative	Absolute		
viral hepatitis	?	-	+	chromosomal abnormalities?
chronic aggressive hepatitis	+	-	+	-
compensated cirrhosis	+	-	+	-
decompensated cirrhosis	-	+	+	-
primary bilious cirrhosis	+	-	+	fetal metastasis
liver cell carcinoma	-	+	+	possible
hemolytic anemias	+	-	+	some forms inherited
intrahepatic cholestasis of pregnancy	-	-	+	-
acute fatty liver of pregnancy	-	+	+	-
DUBIN JOHNSON Syndrome	-	-	+	inherited
ROTOR Syndrome	-	-	+	inherited
GILBERT's Disease	-	-	-	inherited
WILSON's Disease	+	-	+	inherited
Hepatic porphyria	+	-	+	inherited

5. some rare congenital diseases (WILSON's disease or hepatic porphyria)

Questionable is termination with acute viral hepatitis, because the extent of the possible chromosome damage from the virus has not been well defined.

5 Discussion

The discussion of liver disease during pregnancy must emphasize the separation of liver diseases caused by liver diseases specific to the pregnant state from those who occur also outside of pregnancy. Because of the problems with the differential diagnosis of infectious hepatitis from other diseases presenting with jaundice it is justified to

isolate each patient with jaundice until an infectious process has been ruled out.

Since any icteric disease in pregnancy without regard to etiology and pathogenesis is also a considerable risk for the infant, the prenatal surveillance of the fetus must be intense. The question of the necessity for tocolysis with premature onset of labor because of the liver disease must be decided on an individual basis.

Human placental lactogen as an indicator of placental function is not influenced by liver disease. The assay of estriol excretion in the urine or of serum estriol levels is not influenced as long as radio-immune assays are used in contrast to colorimetry [37]. Thus, an existing jaundice does not prevent the use of these parameters for monitoring the intrauterine fetal well-being.

Keywords: Cholestasis of pregnancy, cirrhosis, fatty liver of pregnancy, liver function during normal pregnancy, termination of pregnancy in liver disease, viral hepatitis.

Zusammenfassung

Leberfunktion und Lebererkrankungen während der Schwangerschaft.

Beim Zusammentreffen von Lebererkrankung und Schwangerschaft interessieren zwei Fragen:

1. Wie wird die erkrankte Leber durch die Schwangerschaft beeinflusst?

2. Welche Auswirkungen hat die Lebererkrankung auf die Schwangerschaft?

Diese beiden Fragen sollen an Hand der vorliegenden Literatur beantwortet werden.

Eine normale Schwangerschaft stellt bereits für eine gesunde Leber eine erhebliche funktionelle und metabo-

lische Mehrbelastung dar. Dieses findet seinen Ausdruck in zahlreichen von der Norm abweichenden biochemischen Befunden (Tab. I).

Die Serumenzyme lassen während der Schwangerschaft typische Veränderungen erkennen (Tab. II).

Jede mit Ikterus einhergehende Erkrankung kann auch während der Schwangerschaft auftreten (Ikterus in graviditate). Daneben gibt es Ikterusfälle als Folge der Schwangerschaft (Ikterus e graviditate).

Die Ikterushäufigkeit bei Schwangeren liegt bei 0,2–1,8‰. Ikterus in der Schwangerschaft ist also ein relativ seltenes Symptom.

Eine Übersicht über die Häufigkeit der verschiedenen Ikterusformen ist aus der Tab. III zu entnehmen.

Tab. IV gibt eine Systematik der mit Ikterus einhergehenden Erkrankungen während der Schwangerschaft.

Die akute Virushepatitis stellt die häufigste Form einer Lebererkrankung während der Schwangerschaft dar.

Tab. V gibt eine Übersicht über die verschiedenen Hepatitisserreger. Die Empfänglichkeit für eine akute Hepatitis ist bei der Schwangeren nicht höher als bei der Nichtschwangeren. Auch der Verlauf scheint in der Schwangerschaft nicht anders als außerhalb der Schwangerschaft zu sein.

Die Infektionswege der Hepatitis auf das Kind sind vielfältig; eine diaplazentare Übertragung ist als gesichert anzusehen.

Das Risiko für eine neonatale Infektion wird umso größer, je näher die Hepatitisinfektion der Mutter am Entbindungstermin liegt.

Über die Aborthäufigkeit und die Totgeburtenrate liegen unterschiedliche Angaben vor. Einstimmigkeit herrscht darüber, daß die Frühgeburtenrate auf 15–35% erhöht ist. Die Rate der intrauterinen Mangelentwicklungen ist bei der akuten Hepatitis nicht erhöht. Die Mißbildungshäufigkeit ist nicht vermehrt. Ob fetale Chromosomenschäden bei der akuten Hepatitis auftreten und geburts-hilflich von Bedeutung sein können, ist noch nicht zweifelsfrei bewiesen.

Die akute Virushepatitis stellt insgesamt gesehen keine Indikation zum Schwangerschaftsabbruch dar.

Das gleichzeitige Vorkommen von chronischer Hepatitis und Zirrhose einerseits und einer Schwangerschaft andererseits ist ein seltenes Ereignis. Während die persistierende Form der chronischen Hepatitis in der Schwangerschaft keinen besonderen Verlauf nimmt, ist das bei

der chron.-aggressiven Hepatitis unterschiedlich. Auch der Zirrhoseverlauf kann während der Schwangerschaft sehr unterschiedlich sein. Die Hauptgefahr für die Schwangere besteht bei den chronischen Verlaufsformen in der Hämatemesis bei bereits vorbestehender portaler Hypertension.

Bei den chronischen Hepatiden und der Zirrhose ist die Frühgeburtenrate (bis 50%), die Totgeburtenfrequenz (bis 20%) und auch die postpartale Sterblichkeit erhöht. Die Mißbildungsrate ist nicht erhöht, wohl aber die Abortfrequenz.

Die selteneren Ikterusformen wie Medikamentenikterus, extrahepatische Cholestase und die funktionellen Hyperbilirubinämien (Tab. VI) zeigen während der Schwangerschaft keinen besonderen Verlauf. Eine Indikation zur Abortio ist in diesen Fällen nicht gegeben.

Von den mit Ikterus einhergehenden hämolytischen Anämien können einige in der Schwangerschaft eine progrediente Verschlechterung erfahren und zu hämolytischen Krisen führen. Eine Indikation zum Schwangerschaftsabbruch ist oft gegeben. Die intrahepatische Schwangerschaftscholestase oder der idiopathische Schwangerschaftsikerus ist die zweithäufigste Ikterusform in der Schwangerschaft. Die Ätiologie dieser für die Mutter harmlosen Erkrankung ist noch nicht vollständig geklärt. Die kindliche Prognose ist durch eine Frühgeburtenrate bis 40% getrübt. Eine Indikation zur Abortio ist nicht gegeben.

Die akute Schwangerschaftsfettleber ist ein glücklicherweise seltenes, jedoch schwerstes Krankheitsbild. Bisher sind in der Literatur 118 Fälle beschrieben worden. Diese Schwangerschaftskomplikation tritt erst im III. Trimenon auf. Die Ursache der Erkrankung ist unbekannt. Durch intensive therapeutische Maßnahmen konnte die Sterblichkeit dieser Erkrankung von über 80% auf 45% gesenkt werden.

Die absoluten und relativen Indikationen zum Schwangerschaftsabbruch bei Lebererkrankungen sind in der Tab. VII zusammengestellt.

Da die differentialdiagnostische Abklärung eines Ikterus sehr schwierig sein kann und infektiöse Erkrankungen zahlenmäßig überwiegen, ist es gerechtfertigt, jede Schwangere mit Ikterus so lange zu isolieren, bis der Beweis erbracht ist, daß es sich nicht um ein infektiöses Geschehen handelt.

Schlüsselwörter: Leberfunktion in der normalen Schwangerschaft, Schwangerschaftscholestase, Schwangerschaftsfettleber, Schwangerschaftsabbruch bei Lebererkrankungen, Virushepatitis, Zirrhose.

Résumé

Fonction et maladies hépatiques en cours de grossesse

La coïncidence de maladie du foie et de grossesse soulève les deux principales questions suivantes:

1. Dans quelle mesure la grossesse joue-t-elle un rôle influent sur le foie malade?
2. Quels sont les effets de la maladie du foie sur la grossesse?

Nous nous proposons de répondre à ces deux questions en nous reportant à la littérature.

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Une grossesse normale représente déjà une charge fonctionnelle et métabolique supplémentaire considérable pour un foie sain, ainsi qu'il apparaît dans les nombreux résultats biochimiques s'écartant de la norme (Tab. I). Les enzymes du sérum montrent des changements typiques pendant la grossesse (Tab. II).

Toute maladie liée à l'ictère est possible pendant la grossesse (ikterus in graviditate). De plus, il existe des cas d'ictère consécutifs à la grossesse (ikterus e graviditate).

La fréquence d'ictère chez les femmes enceintes est de 0,2 à 1,8‰. L'ictère en cours de grossesse est donc un symptôme relativement rare.

Un aperçu de la fréquence des diverses formes d'ictère est donné Tab. III.

Le Tab. IV donne un classement des maladies liées à l'ictère pendant la grossesse.

L'hépatite virale aiguë représente la forme la plus fréquente des maladies du foie en cours de grossesse. Le Tab. V offre un tableau des divers agents de l'hépatite. La réceptivité pour une hépatite aiguë n'est pas plus élevée chez les femmes enceintes que chez celles non enceintes. De même, le déroulement de cette hépatopathie ne semble pas différer entre la grossesse et la non-grossesse.

Les voies infectieuses communiquant l'hépatite à l'enfant sont nombreuses; une transmission diaplasentaire ne semble plus faire de doute.

Le risque d'une infection néonatale est d'autant plus grand que l'infection hépatique de la mère est proche du terme de l'accouchement.

Les données diffèrent sur la fréquence des avortements spontanés et le taux des morts-nés. Mais elles concordent sur l'augmentation du taux des naissances prématurées à 15-35%. Le taux des malnutritions intra-utérines n'est pas plus élevé dans les cas d'hépatite aiguë. Il en est de même pour la fréquence des malformations. La question concernant l'apparition de lésions chromosomiques fœtales en cas d'hépatite aiguë et de leur importance en obstétrique reste encore en suspens. L'hépatite virale aiguë ne comporte d'une façon générale aucune indication d'interruption de grossesse.

L'apparition simultanée d'hépatite chronique et de cirrhose d'une part et d'une grossesse d'autre part est un fait rare. Tandis que la forme persistante de l'hépatite chronique dans la grossesse ne suit pas un cours particulier, il peut en aller autrement pour l'hépatite chron.-agressive. De même, l'évolution de la cirrhose peut être très différenciée pendant la grossesse. Le risque principal encouru par la femme enceinte est causé par les formes

évolutives chroniques de l'hématémèse en cas d'hypertension portale déjà présente.

Dans les hépatites chroniques et la cirrhose, le taux des naissances prématurées (jusqu'à 50!), la fréquence des morts-nés (jusqu'à 20!) ainsi que la mortalité postpartale sont élevés. Le taux des malformations n'augmente pas, au contraire de celui des avortements spontanés.

Les formes plus rares d'ictère, telles que l'ictère médicamenteux, la cholestase extra-hépatique et l'hyperbilirubinémie fonctionnelle (Tab. VI) ne montrent aucun cours particulier pendant la grossesse. Une indication d'interruption n'est pas donnée dans ces cas.

Certaines des anémies hémolytiques avec ictère peuvent, pendant la grossesse, subir une aggravation progressive et provoquer des crises hémolytiques. Une interruption de grossesse est souvent indiquée.

La cholestase gravidique intra-hépatique ou l'ictère gravidique protopathique représente la deuxième forme ictérique la plus fréquente en cours de grossesse. L'étiologie de cette maladie sans danger pour la mère n'a pas encore été entièrement éclaircie. Le pronostic pour l'enfant reste insatisfaisant à cause du taux des naissances prématurées qui peut atteindre 40!. Une indication d'interruption n'est pas donnée.

La cirrhose gravidique aiguë est une forme de maladie très grave, heureusement rare. 118 cas ont été rapportés dans la littérature jusqu'à présent. Cette complication de la grossesse n'apparaît qu'au III^{ème} trimestre et la cause en est inconnue. Des mesures thérapeutiques intensives ont permis d'abaisser de plus de 80 à 45% le taux de la mortalité due à cette maladie.

Les indications absolues et relatives d'une interruption de grossesse dans les cas de maladies hépatiques ont été répertoriées Tab. VII.

Le diagnostic différentiel d'un ictère pouvant être très difficile à établir et la proportion des maladies infectieuses étant supérieure, il apparaît justifié d'isoler toute femme enceinte atteinte d'ictère jusqu'à ce qu'on ait pu prouver qu'il ne s'agit pas d'un cas infectieux.

Mots-clés: Cholestase gravidique, cirrhose, cirrhose gravidique, fonction hépatique dans la grossesse normale, hépatite virale, interruption de grossesse en cas de maladies hépatiques.

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Received and accepted August 2, 1978.

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